DOI:
10.1016/j.schres.2014.03.032

Document Version
Peer reviewed version

It is All in the Factors: Effects of Cognitive Remediation on Symptom Dimensions

Matteo Cella[1], *Clare Reeder*[1], *Til Wykes*[1]

[1] *King's College London, Institute of Psychiatry, London, UK*

Corresponding author:

Dr. Matteo Cella

Department of Psychology,

Institute of Psychiatry,

King's College London,

De Crespigny Park,

SE5 8AF

London, UK

Telephone: (+44) 020 7848 5001

Fax: (+44) 020 7848 0334

Abstract

Background: Cognitive Remediation (CR) aims primarily to improve cognition and functional outcomes. However, a limited number of studies reported a positive effect on symptoms. This limited effect may be because the symptom clusters considered are too broad and heterogeneous. This study explores, for the first time, the effect of CR on five empirically defined symptom dimensions of schizophrenia.

Method: Participants were patients with schizophrenia taking part in a randomised controlled trial comparing CR plus treatment as usual (CR, N=43) to treatment as usual (TAU, N=42). All participants were assessed at baseline and 14-weeks (i.e. at the conclusion of treatment for the CR group) with the Positive and Negative Symptoms Scale (PANSS). Five symptoms dimensions were derived from the PANSS scores: Positive (POS), Negative (NEG), Disorganised (DIS), Excited (EXC) and Emotional Distressed (EMD).

Results: After CR, the therapy group had a significant reduction in DIS and NEG symptom dimensions compared to the TAU group. The traditional PANSS factors showed no effect of CR on symptoms.

Conclusion: CR can have a positive effect on disorganisation but also on negative symptoms. Using detailed symptom dimensions can characterise more accurately the effect of CR on symptom of schizophrenia.

Keywords: Cognitive Remediation; Cognition; Positive symptoms; Negative symptoms**;** PANSS.

Introduction

Although not an elective target for Cognitive Remediation (CR), a number studies have reported that CR has a small effect on symptoms of schizophrenia (Wykes et al., 2011). The majority of studies reporting a positive effect found that CR reduced negative symptoms (Klingberg et al., 2011; Gharaeipour et al 2012). The effect of CR on negative symptoms is consistent with a few reports of an association between negative symptoms and cognitive problems (Milev et al., 2005; Ventura et al., 2009).

Symptom assessment in CR studies is generally conducted for screening purposes and considered as a secondary outcome. The majority of studies assessed symptoms with the Positive and Negative Syndrome Scale (PANSS) using the original distinction proposed between positive, negative and general symptoms (Kay et al., 1987). In the last two decades an intense debate on the PANSS factorial structure advanced a number of new empirically based factorial solutions (White, 2005). Most of these factor analytic studies suggest that the PANSS should be considered as a 5-factor scale, but there is little consensus on item loading and factor names (Emsley et al., 2003; Lancon et al., 2000). Notably, Van der Gaag and colleagues (2006) attempted a resolution of this debate by considering all the 25 five-factor solutions published but a stronger solution failed to emerge. More recently, Wallwork et al., (2012), advanced a five-factor consensus solution based on the most reliable items found across all the solutions published. This solution has proven reliable and likely to accommodate all the discrepancies that analytic techniques could not account for (Rodriguez-Jimenez et al., 2013).

In this study we explore whether the consensus 5-factor structure advanced by Wallwork et al., (2012) can better capture changes following a course of CR compared to the traditional 3-factor solution. No previous study has ever explored the effect of CR beyond the positive, negative and general symptoms distinction proposed in the original version of the PANSS (Kay et al., 1987). The 5-factor structure used here can provide additional knowledge in two important areas. Firstly, it will explore, for the first time, the effect of CR on symptoms dimensions such as, mood, excitement and disorganization with this latter dimension measuring a problem area likely to be affected by CR. Secondly, assess the

relevance of using empirically validated factor solutions for positive and negative dimensions as opposed to the conventional items.

Method

Study design

The data for this study were from a single blind randomised controlled trial of cognitive remediation plus treatment-as-usual (CR) versus a treatment-as-usual (TAU) control. Assessments of cognition, symptoms and functioning were carried out at week 0 and 14. For further details of the trial design see Wykes et al., (2007). Trial Registration: ISRCTN44277627 [controlled-trials.com].

Participants

Eighty five participants were recruited from community mental health teams in South London, UK. Inclusion criteria: (i) DSM-IV diagnosis of schizophrenia, (ii) aged 17 - 66, (iii) evidence of executive or memory problems (more than one standard deviation below the normative mean on the Rivermead Behavioural Memory Test (Wilson et al., 1999), Hayling Test or the Wisconsin Card Sorting Task (Heaton et al., 1993; Burgess and Shallice, 1996). Exclusion criteria: (i) current plans to change medication, (ii) evidence of a premorbid learning disability, (iii) primary DSM-IV substance abuse, or (iv) evidence of head injury or organic disorder. Five participants (i.e. 2 in the CR and 3 in the TAU group) did not complete the PANSS and/or left the study and could not be included in the analysis.

Measures

Positive and negative syndrome scale (*PANSS, Kay et al., 1987)*

This is a 30-item measure of symptom severity for schizophrenia. The measure is administered as a clinical interview by a trained researcher or clinician. Each item can be scored on a 7-point scale ranging from not symptomatic (i.e. 1) to extremely severe symptom (i.e. 7). For this study we first scored the PANSS according to Kay et al (1987) and used its three factors: Positive (K_Pos), Negative (K_Neg) and General (K_Gen). We also

scored the PANSS according to Wallwork et al., (2012) and extracted five factors: Positive Symptoms (W_Pos), Negative Symptoms (W_Neg), Disorganised (W_Dis), Excited (W_Exc) and Negative Emotion Depressed (W_Emd). W_Pos included four items (i.e. P1, P3, P5 and G9); W_Neg included six items (i.e. N1, N2, N3, N4, N6 and G7); W_Dis included four items (i.e. P2, N5, G10 and G11); W_Exc included four items (i.e. P4, P7, G8 and G14); W_Emd included three items (i.e. G2, G3 and G6).

Therapy

This is a 40 session individual therapy involving a number of tasks targeting executive function, attention, working memory and long-term memory (Wykes & Reeder, 2005). It takes place at least three days per week and is conducted by trained graduate psychologists. The intervention is manual-based but sessions are tailored to the individual, according to their cognitive strengths and difficulties, and gradually increase in difficulty over the course of therapy. Sessions comprise a series of tasks which are highly repetitive and taught using errorless learning and scaffolding training techniques. The therapy aims to improve the participant's approach to tasks so that it becomes systematic, organised and highly strategic. The therapy also emphasises the importance of metacognitive knowledge of cognitive strengths and difficulties and encourages participants to transfer new cognitive skills to everyday life (see Wykes & Reeder, 2005 for further details).

Analysis

ANCOVA was used to explore the effect of therapy on each of the symptom factors according to the solution proposed by Kay et al., (1987) and Wallwork et al., (2012). Level of symptom at post-therapy was entered as a dependent variable and, therapy group was entered as the independent variable. Baseline symptom level was entered in the model as covariate.

Results

At baseline participants in the CR group had comparable levels of symptoms compared to participants in the TAU group (Table 1). The effects of cognitive remediation on objective cognitive measures are reported in Wykes et al., (2007).

----- Table 1 about here----

ANCOVA conducted to investigate the effect of CR on the factors proposed by Kay et al., 1987 yield no significant difference between the groups. Amongst the factors proposed by Kay et al., the best fitting model was for K_Neg, $F(2, 80)=3.3$, $p=0.08$, partial $\eta^2=0.03$.

The same analysis conducted for the Wallwork et al., factors showed no significant interaction between therapy group and factor for W_Pos, W_Exc and W_Emd (all models $p>0.05$). Differently models conducted for negative symptoms and cognitive disorganisation showed significant change in favour of the CR group: W_Neg, $F(2, 80)=21.1$, $p<.0001$, partial $\eta^2=0.07$, and W_Dis, $F(2, 80)=14.2$, $p<.0001$, partial $\eta^2=0.1$.

Discussion

The results of this study demonstrated that CR can have a positive impact on particular symptom domains of schizophrenia. In this study we assessed symptoms domains using the two factorial solutions of the PANSS: the solution originally proposed by Kay et al., (1987) and a more recent consensus 5-factor solution proposed by Wallwork et al., (2012). The Wallwork and colleagues solution provides a more refined description of symptom dimensions compared to the traditional 3-factor solution. In particular, the inclusion of a disorganisation factor seems relevant for the evaluation of CR programs as improvement in this domain is expected and may mirror functional improvements.

In line with some previous studies the current results showed an effect of CR on the negative symptoms cluster (Klingberg et al., 2011; Gharaeipour et al., 2012). The relationship between negative symptoms and cognitive problems is variably reported in the literature and may be largely influenced by the type of symptoms considered (Harvey et al., 2006; Ventura et al., 2010). Our results show that this relationship may only be apparent when considering a narrower and more homogeneous set of symptoms. The solution

proposed by Wallwork et al (2012) includes in the negative factor items from the general complex (e.g. motor retardation) and excluding items related to cognitive processes (e.g. difficult in abstraction). The items in this solution appear to define more precisely the behavioural and the expressive elements of negative symptoms and provide an assessment of this domain better aligned with recent empirical findings (Daneluzzo et al., 2002; Messinger, 2011; Liemburg et al., 2013).

Perhaps unsurprisingly, as this appears as the most "cognitive" symptoms cluster, W_Dis scores significantly reduce following CR. This is the first time that a CR study showed changes in this domain. Reducing levels of disorganization is part of what CR is ultimately aiming to achieve as part of its larger goal of promoting community functioning. A possible reason for the improvement in this symptom complex could be the strategic approach promoted as part of the CR program used here (Wykes & Reeder, 2005; Cella et al., in press). Changes in this dimension would be quite difficult to observe in the traditional PANSS structure as the W_Dis factor items are drawn from the positive (e.g. conceptual disorganisation), negative (e.g. difficult in abstraction) and general scale (e.g. poor attention). The current findings also suggest that the measurement of gross cognitive problems could be achieved using clinical interviews. Clinicians may consider using these PANSS items to assess CR programs targeting disorganization in addition to neuropsychological testing. This can be particularly helpful in for screening and interventions targeting the early and prodromal phase of psychosis (Demjaha et al., 2012).

This study has limitations. The sample is considered is not very large but enough to appreciate differences. These findings would need to be replicated in other studies before a clear recommendation on the use of the PANSS 5-factor structure can be advanced, particularly because the effect sizes are modest. Our findings are also limited to the type of CR used and may not extend other programs with reduced therapist contact.

In summary, the results of this study suggest that when specific symptoms dimensions are considered it is possible to observe a positive effect of CR. The 5-factor solution used in this study defines more precise and homogeneous symptoms dimensions which may be more appropriate to evaluate CR effectiveness. The results also show that reduction in disorganisation and negative symptoms could be expected after CR.

References

Burgess, P., Shallice,T., 1996. Response suppression, initiation and strategy use following frontal lobe lesions. Neuropsychologia, 34, 263:273.

Cella M, Bishara AJ, Medin E, Swan S, Reeder C, Wykes T. Identifying Cognitive Remediation Change Through Computational Modelling-Effects on Reinforcement Learning in Schizophrenia. Schizophr Bull. (In press).

Daneluzzo, E., Arduini, L., Rinaldi, O., Di Domenico, M., Petruzzi, C., Kalyvoka, A., Rossi, A. 2002. PANSS factors and scores in schizophrenic and bipolar disorders during an index acute episode: a further analysis of the cognitive component. Schizophr Res. 56:129-36.

Demjaha, A., Valmaggia, L., Stahl, D., Byrne, M., McGuire, P. 2012. Disorganization/cognitive and negative symptom dimensions in the at-risk mental state predict subsequent transition to psychosis. Schizophr Bull. 38:351-9.

Emsley, R., Rabinowitz, J., Torreman, M., 2003. The factor structure for the Positive and negative syndrome scale (PANSS) in recent-onset psychosis. Schizophr. Res., 61, 47–57.

Gharaeipour, M., Scott, B., 2012. Effects of cognitive remediation on neurocognitive functions and psychiatric symptoms in schizophrenia inpatients. Schizophr. Res. 142, 165-70.

Harvey, P.D., Koren, D., Reichenberg, A., Bowie, C.R., 2006. Negative symptoms and cognitive deficits: what is the nature of their relationship? Schizophr. Bull. 32, 250-8.

Heaton, R.K., Chelune, G.J., Talley, J.L., Kay, G.G., Curtiss, G., 1993. Wisconsin Card Sorting Test manual: Revised and Expanded. Odessa, FL: Psychological Assessment Resources.

Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The Positive and Negative Syndrome Scale(PANSS) for Schizophrenia. Schizophr. Bull. 13, 261–276.

Klingberg, S., Wölwer, W., Engel, C., Wittorf, A., Herrlich, J., Meisner, C., Buchkremer, G., Wiedemann, G., 2011. Negative symptoms of schizophrenia as primary target of cognitive behavioral therapy: results of the randomized clinical TONES study. Schizophr Bull. 37, S98-110.

Lancon, C. Auquier P., G.Nayt,. Reine, G., 2000. Stability of the five-factor structure of the positive and negative syndrome scale (PANSS) Schizoph. Res. 42, 231–239.

Liemburg, E., Castelein, S., Stewart, R., van der Gaag, M., Aleman, A., Knegtering, H., Genetic Risk and Outcome of Psychosis (GROUP) Investigators, 2013. Two subdomains of negative symptoms in psychotic disorders: established and confirmed in two large cohorts. J. Psychiatr. Res. 47, 718-25.

Messinger, J.W., Trémeau, F., Antonius, D., Mendelsohn, E., Prudent, V., Stanford, A.D., Malaspina, D., 2011. Avolition and expressive deficits capture negative symptom phenomenology: implications for DSM-5 and schizophrenia research. Clin. Psychol. Rev., 31, 161-8.

Milev, P., Ho, B.C., Arndt, S., Andreasen, N.C., 2005. Predictive values of neurocognition and negative symptoms on functional outcome in schizophrenia: a longitudinal first-episode study with 7-year follow-up. Am J Psychiatry., 162:495–506.

Rodriguez-Jimenez, R., Bagney, A., Mezquita, L., Martinez-Gras, I., Sanchez-Morla, E.M., Mesa, N., Ibañez, M.I., Diez-Martin, J., Jimenez-Arriero, M.A., Lobo, A., Santos, J.L., Palomo, T., 2013. Cognition and the five-factor model of the positive and negative syndrome scale in schizophrenia. Schizophr. Res. 143, 77-83.

van der Gaag, M., Cuijpers, A., Hoffman, T., Remijsen, M., Hijman, R., de Haan, L., van Meijel, B., van Harten, P.N., Valmaggia, L., de Hert, M., Wiersma, D., 2006. The five-factor model of the Positive and Negative Syndrome Scale I: Confirmatory factor analysis fails to confirm 25 published five-factor solutions. Schizophr. Res. 85, 273–279.

Ventura, J., Hellemann, G.S., Thames, A.D., Koellner, V., Nuechterlein, K.H., 2009. Symptoms as mediators of the relationship between neurocognition and functional outcome in schizophrenia: a meta-analysis. Schizophr. Res. 113, 189–199.

Ventura, J., Thames, A.D., Wood, R.C., Guzik, L.H., Hellemann, G.S. 2010. Disorganization and reality distortion in schizophrenia: a meta-analysis of the relationship between positive symptoms and neurocognitive deficits. Schizophr Res. 121:1-14.

Wallwork, R.S., Fortgang, R., Hashimoto, R., Weinberger, D.R., Dickinson, D., 2012. Searching for a consensus five-factor model of the Positive and Negative Syndrome Scale for schizophrenia. Schizophr. Res. 137, 246-50.

White, L., 2005. Interpreting the PANSS: measures, factors and models. Schizophr. Res., 79, 349–351.

Wilson, B., Clare, L., Cockburn, J., Baddeley, A., 1999. Rivermead Behavioural Memory Test. Thames Valley Test Company.

Wykes, T., Huddy, V., Cellard, C., McGurk, S.R., Czobor, P. A 2011. Meta-analysis of cognitive remediation for schizophrenia: methodology and effect sizes. Am J Psychiatry. 168, 472-85.

Wykes. T., Reeder, C., Landau, S., Everitt, B., Knapp, M., Patel, A., Romeo, R., 2007. Cognitive remediation therapy in schizophrenia: randomised controlled trial. Br J Psychiatry, 190, 421-7.

Wykes, T., Reeder, C., 2005. Cognitive remediation therapy for schizophrenia: Theory and practice. London: Brunner Routledge.

Table 1

Table 1 Mean (SD) baseline and post-treatment values for PANSS Kay et al., (1987) three factors and Wallwork et al., (2012) five factors.

PANSS factor	Baseline		Post-treatment	
	CRT (N=43)	TAU (N=42)	CRT (N=41)	TAU (N=39)
K_Pos	14.2 (5.4)	12.5 (4.9)	14.2 (5.4)	13.8 (6.4)
K_Neg	18.6 (7.3)	16.6(7.2)	17.0 (6.6)	16.7 (7.1)
K_Gen	30.1 (8.2)	27.5 (6.8)	27.4 (10.1)	29 (8.5)
W_Pos	8.31 (4.1)	7.3 (3.6)	9.1 (5.5)	8.8 (5.2)
W_Neg	15.4 (6.5)	13.2 (6.3)	13.6 (5.6)	13.7 (5.5)
W_Dis	8.3 (3.1)	8.2 (2.6)	7 (2.3)	8.3 (2.8)
W_Exc	5.4 (2.1)	5.3 (2.4)	5.5 (2.4)	5.6 (2.7)
W_Emd	5.3 (2.6)	5.5 (2.4)	5.6 (3.2)	5.8 (2.1)

Note: Kay et al., factors: Positive (K_Pos), Negative (K_Neg) and General (K_Gen). Wallwork et al., factors: Positive (W_Pos), Negative (W_Neg), Disorganised (W_Dis), Excited (W_Exc) and Negative Emotion Depressed (W_Emd).

Acknowledgement

The authors would like to acknowledge the support of the NIHR Biomedical Sciences Centre in Mental Health at the South London and Maudsley Foundation Trust and Institute of Psychiatry, King's College London. TW would like to acknowledge the NIHR for her Senior Investigator Award.

***Conflict of Interest**

None

***Contributors**

TW and CR secured funding and conducted the original study. MC did the analyses. MC and TW wrote the first draft of the paper. All authors contributed to the final version and have approved the final manuscript.